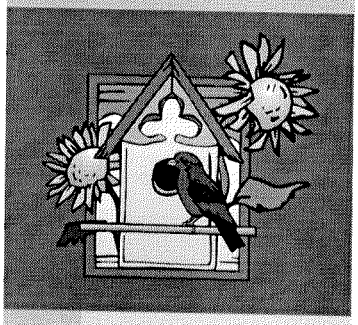
March/April 2002

Editor:
Jean Eilertson, PharmD



The Apothecary Bulletin

PHARMACY SERVICE & THERAPEUTICS COMMITTEES
US ARMY MEDDAC, FORT CARSON, COLORADO

FORMULARY CHANGES

The Pikes Peak Region Formulary Committee met on 7 March 2002 and the Evans Pharmacy & Therapeutics (P&T) Committee met on 12 March 2002 with the following medications ***added*** to the Formulary:

+ budesonide 3mg micronized capsules (*Entocort EC*) - for the treatment of mild-to-moderate active Crohn's disease involving the ileum and/or the ascending colon; treatment for up to 8 weeks
+ lansoprazole 15mg and 30mg capsules (*Prevacid*) - use must follow Evans' *GERD Guideline* (see related article)

The following medication was ***deleted*** from the Formulary:

- quinidine 200mg tablets

The Pikes Peak Region Formulary Committee reviewed dermatologic and ophthalmic agents - no changes were made to the Formulary. As part of this ongoing drug class review process, the Committee (with representatives from the Air Force Academy, Peterson AFB, and Evans) will conduct reviews as follows:

May 2002 = oral anti-infective agents
July 2002 (meeting will be 27 June) = cardiovascular agents
September 2002 = endocrine/hematologic agents
November 2002 = gastrointestinal/renal/genitourinary agents
January 2003 = central nervous system agents
March 2003 = dermatologic/ophthalmologic agents

Pharmaceuticals submitted for Formulary consideration will be reviewed based on the above schedule. If a medication is a new entity, it may be considered earlier if submitted via a New Drug Request. Providers desiring to have input into the drug class reviews are encouraged to contact one of the Pikes Peak Committee members: **LTC Edward Torkilson (Pharmacy), MAJ Robert Gray (Family Practice), and Dr. Garold Paul (Internal Medicine).**

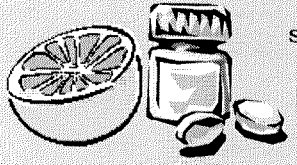
The next Formulary Committee Meetings will be held on Thursday, 1 May (Pikes Peak), and Tuesday, 7 May (Evans' P&T). New Drug Requests must be received by the Chief, Pharmacy

17 to 23 March is . . .
National Poison Prevention Week

A Patient Education Display is
located in the pharmacy waiting area
(will remain available until mid-April)

Q & A

What is the mechanism for drug-grapefruit juice interactions and which medications are involved?



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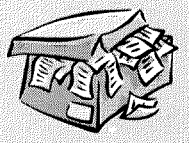
PREVACID ADDED TO FORMUARLY

At the March Pikes Peak Region Formulary Committee meeting, *Prevacid* (lansoprazole) was added to the Formulary for use as an additional step in the ***GERD Guideline*, attached at Enclosure 1**. If a patient is not controlled on *Aciphex* 40mg daily, *Prevacid* will be the next step for GERD therapy before *Prilosec* (**nonformulary - internal use approved if compliance with GERD Guideline**).

Use of these guidelines have the potential to save our facility a sizeable sum of money. Costs per 30 days of therapy are as follows:

Agent	Cost per month
Aciphex 20mg daily	$6.60
Aciphex 40mg daily	$13.20
Prevacid 30mg daily	$29.33
Prilosec 20mg daily	$61.60
Prilosec 20mg twice daily	$123.20

"It's income tax time again,
Americans:
time to gather up those receipts,
get out those tax forms,
sharpen up that pencil,
and stab yourself in the aorta."
~ Dave Barry



NEW GUIDELINES

The American Heart Association (AHA) and the American College of Cardiology (ACC) have updated their practice guidelines for the management of unstable angina reflecting the latest clinical knowledge. Highlights of the revision:

- abciximab - use is downgraded except in patients having an invasive procedure such as balloon angioplasty or stenting
- clopidogrel is recommended, in addition to aspirin and heparin, in nearly all patients with unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI)
- strong recommendation that, shortly after admission, high-risk patients have cardiac catheterization
- recommendation for statins for patients with elevated LDL

The guidelines are posted on the ACC and AHA websites:

www.acc.org
www.americanheart.org

The American Pain Society (APS) released its new clinical guideline for treating acute and chronic pain associated with arthritis. The guideline emphasizes arthritis pain is best treated through a combination of ongoing pain assessment, medication, proper nutrition, exercise, and patient and family education. The guidelines can be found at APS's website:

A Bit of History

- 3500 B.C. -- Earliest historical record of the production of alcohol: the description of a brewery in an Egyptian papyrus.
- 2000 B.C. -- Earliest record of prohibitionist teaching, by an Egyptian priest, who writes to his pupil: "I, thy superior, forbid thee to go to the tavern. Thou art degraded like beasts."
- In 1698, the first patent given to a medicine was granted in England to the makers of Epsom salts.
- In 1802, Proust extracted dextrose from grape juice.
- The gelatin coating of tablets was first described by the French pharmacist Garot in 1838.
- The laxative effect of phenolphthalein was discovered in 1902 by Vamossy, when he was studying it as a possible additive to artificial wines. In 1953, it was introduced as a laxative preparation.
- In 1935, Warburg and associates obtained nicotinamide from a co-enzyme isolated from the red blood cells of a horse.
- In 1938, Anderson first described cystic fibrosis.
- Although chancroid was considered an ancient

NEW INDICATIONS/DRUGS

The FDA has approved *Rebif* (interferon beta-1a) for the treatment of relapsing forms of multiple sclerosis, based on the PRISMS and EVIDENCE studies. In the treatment of relapsing forms of MS, *Rebif* decreases the frequency of clinical exacerbations and delays the accumulation of physical disability.

The FDA has approved *Risperdal* (risperidone) for delaying relapse in the long-term treatment of schizophrenia.

The FDA has approved *Plavix* (clopidogrel) for use in acute coronary syndrome (ACS), based on the results of the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study which was published in August 2001 in *The*

Q & A

Grapefruit juice is a potent inhibitor of the intestinal cytochrome P450 (CYP450) 3A4 system. Interactions with medications can lead to increased bioavailability thereby resulting in increased serum drug levels. In 1989, by chance, investigators observed a food-drug interaction between felodipine and grapefruit juice in a study of felodipine and ethanol in which grapefruit juice was used to mask the taste of ethanol. Additional studies confirmed this interaction. It is thought that grapefruit juice acts on the cytochrome P450 system at the **intestinal level versus that hepatic level.** Recurrent ingestion of grapefruit juice (contains various bioflavonoids) leads to a selective decrease of both CYP3A4 and CYP3A5 protein expression in enterocytes, which results in increased drug bioavailability. A 47% reduction in intestinal CYP3A4 concentration occurs within 4 hours of ingestion of grapefruit juice, and the juice maintains its bioavailability-enhancing effect for up to 24 hours. Studies looking at the quantity of juice consumed suggest that "normal consumption" (up to 3 glasses per day) seems to have intestinal activity only, and consumption of very large quantities (6 to 8 glasses per day) may lead to inhibition of hepatic CYP3A4 also.

Drugs (**not an all inclusive list**) which ***may*** exhibit a drug-food interaction with grapefruit juice include:

calcium channel blockers: amlodipine, felodipine, nifedipine, nicardipine, nimodipine, nisoldipine, diltiazem, verapamil (can result in symptomatic hypotension)

immunosuppressants: cyclosporine, tacrolimus

HMG-CoA reductase inhibitors ("statins"): atorvastatin, lovastatin, simvastatin (can increase risk for rhabdomyolysis)

HIV protease inhibitors: saquinavir

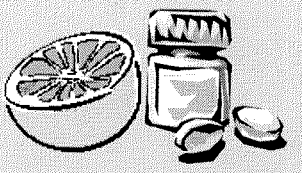
antihistamines: astemizole, terfenadine (can result in QT prolongation)

benzodiazepines: diazepam, midazolam, triazolam (can result in excessive sedation)

other psychiatric medications: buspirone, carbamazepine, clomipramine, sertraline

prokinetic agents: cisapride (can result in QT prolongation)

others: ethinyl estradiol, methadone, sildenafil



Reference: Drug-Grapefruit Juice Interactions, *Mayo Clin Proc*, 2000: 75:933-942

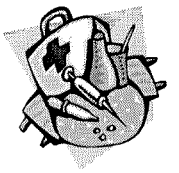
"Laughter is an instant vacation!"
~ Milton Berle

April is National STD Awareness Month

From National Institutes of Health, December 1998:

- In the U.S., an estimated 15.3 million new cases of sexually transmitted diseases (STDs) occur each year, at least one-quarter of them among teenagers.
- Of the top 11 reportable diseases in the U.S. in 1996, five are transmitted sexually (chlamydial infection, gonorrhea, AIDS, syphilis, and hepatitis B).
- Approximately two-thirds of people who acquire STDs in the U.S. are younger than 25.
- In the U.S. in 1994, approximately $10 billion was spent on major STDs (other than HIV/AIDS) and their preventable complications; rises to approximately $17 billion if sexually transmitted HIV infections are included.
- Worldwide, an estimated 333 million new cases of four curable STDs (gonorrhea, chlamydial infection,

ADVERSE DRUG REACTION REPORT

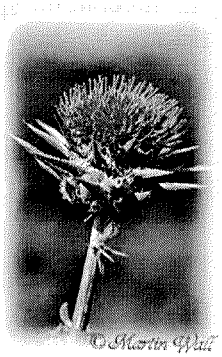


There were 52 adverse drug reactions (ADRs) documented for January (n=28) and February (n=24), of which 18 (35%) were reported **spontaneously** (5 from Family Practice; 4 each from Internal Medicine and pharmacy; 2 from 5E; and 1 each from General Surgery, PACC, and Preventive Medicine). The most prevalent adverse events involved the anti-infective agents (n=18; 35%), the psychotherapeutic agents (n=9; 17%), the analgesic agents (n=7; 13%), and the cardiovascular agents (n=6; 12%). The anti-infective agents continue to be the top medication class involved in the reported adverse events. The rate of outpatient ADR reporting has remained consistent over the last year.

Two events were deemed moderate on the severity scale (mild, moderate, severe, fatal): (1) a 69 year old female hospitalized for acute renal failure with acute tubular necrosis with additional diagnosis of chronic renal insufficiency likely due to NSAID use, and (2) a 59 year old male hospitalized for allergic pneumonitis possibly due to *Levaquin.*

Thank you to all health care personnel who

HERB OF THE (every other) MONTH



The use of milk thistle (*silybum marianum* family; also known as Marian Thistle, Our Lady's Thistle, St. Mary's Thistle) dates back over 2,000 years. Ancient Greek texts refer to the use of milk thistle as a liver protectant. Pliny the Elder, a first century Roman writer (23-79 A.D.), noted that the plant's juice was excellent for "carrying off bile". In 19th century Europe, it was used for varicose veins, menstrual difficulty, and liver/spleen/kidney ailments. Westmacott wrote in 1694, "*It is a friend to the liver and blood: the prickles cut off, they were formerly used to be boiled in the Spring and eaten with other herbs; but as the World decays, so doth the use of good old things and others more delicate and less virtuous brought in.*" In homeopathy, a tincture of the seeds has been used to treat liver disorders, jaundice, gallstones, peritonitis, hemorrhage, bronchitis, and varicose veins. In Europe, milk thistle is widely used to treat various liver diseases including cirrhosis, hepatitis, and chemical- or alcohol-induced fatty liver. It is also used for Death Cap mushroom poisonings - silymarin binds to liver cells preventing mushroom poisons from binding, blocking poisonous effects.

Milk thistle, which blooms from June to August, is a fine, tall plant with a long stem, green leaves with white spots, and a pink to purple spiky flowered head (resembles a thistle). It is native to the Mediterranean and grows wild throughout Europe, North America, and Australia. The active ingredient of milk thistle, silymarin, first isolated by German scientists in 1968, is a mixture of three isomeric flavonolignans. The leaves and stem of the plant are edible and can be used in salads or eaten raw.

Although the mechanism of action is not clearly understood, the primary activities of milk thistle are as a hepatoprotectant and as an antioxidant. Mechanisms attributed to milk thistle include: increased protein synthesis in liver cells due to increased activity of rRNA (contains a steroid structure that stimulates DNA and RNA synthesis resulting in activation of the regenerative capacity of the liver through cell development), altered outer liver cell membrane structure thereby halting entrance of toxins into the cell (silymarin has the ability to block the toxin's binding sites), and antioxidant properties by scavenging pro-oxidant free radicals and increasing intracellular concentrations of glutathione.

Because silymarin is poorly absorbed, it must be concentrated for oral use. The usual dose of milk thistle extract is between 300mg and 600mg daily for products standardized with 70-80% silymarin content (average daily doses of 200mg to 400mg). Human studies have shown few adverse effects. Brief disturbances of GI function (loose stools, upset stomach, increased gas) have been reported but rarely resulted in discontinuation of treatment. Mild allergic reactions have also been reported.

WEBSITES OF INTEREST

http://evans.amedd.army.mil – Evans' page
http://evans.amedd.army.mil/pharmnew/ — Evans' pharmacy website; access to the Formulary
http://www.pec.ha.osd.mil – DoD Pharmacoeconomic Center, Ft Sam Houston
http://www.cs.amedd.army.mil/qmo/pguide.htm – DoD/VHA Practice Guidelines; current guidelines include Low Back Pain, Asthma, Diabetes, COPD, Hypertension, Hyperlipidemia, Tobacco Use Cessation, Major Depressive Disorder, Dysuria in Women

Poison Prevention Websites

http://www.rmpdc.org/ — Rocky Mountain Poison and Drug Center
http://www.poisonprevention.org/index.html — Poison Prevention Week Council
http://www.aapcc.org/ — American Association of Poison Control Centers
http://wellness.ucdavis.edu/safety_info/index.html — UC Davis Health System Wellness Center; download their *California Poison Control System Answer Book*
http://www.cdc.gov/ncipc/dacrrdp/spotlite/poison.htm — Center for Disease Control and Prevention's National Center for Injury Prevention and Control
http://www.cpsc.gov/cpscpub/pubs/386.html — Consumer Product Safety Commission
http://checc.sph.unc.edu/rooms/library/lead/ — The Environmental Resource Program at UNC-Chapel Hill's Childhood Lead Poisoning Prevention Site with links to other websites on this subject

IN THE LITERATURE...

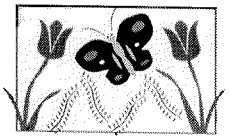
In the March issue of *Lancet*, vol 359, a group of investigators from the Sticht Center for Aging at Wake Forest University, North Carolina, assessed three-year rates of decline in strength of extensor muscle around the knee and walking-speed in 641 women with hypertension in the Women's Health and Aging Study. The women were stratified into four groups depending on type and duration of antihypertensive drug treatment. Women who were continuous users of angiotensin-converting enzyme inhibitors (ACEI) had a lower average three-year decline in muscle strength of 1kg compared with a decline of 3.7kg in continuous/intermittent users of other antihypertensive drugs. Women who had never used antihypertensive drugs had an average decline in muscle strength of 3.9kg. Also, women who used ACEI continually had a smaller reduction in three-year walking speed (1.7cm/sec) compared with intermittent users (13.9cm/sec). Three-year walking speed reduction was greater in intermittent users of other antihypertensive drugs (15.7cm/sec) and for women who did not use antihypertensive drugs at all (17.9cm/sec). ***The investigators stated that a randomized, controlled trial is needed to confirm their findings.***

Researchers at the State University of New York along with researchers in France studied 4,714 hypertensive men who were treated by their physicians and who had a standard health checkup at the Center in Paris between 1972 and 1988. CVD and CHD mortality were assessed for a mean period of 14 years. The results of the study were reported in the March issue of *Archives of Internal Medicine*, vol 162. The investigators reported that the most important result of their study is that cardiovascular mortality, especially CHD mortality, is much higher in uncontrolled hypertensive men than in controlled hypertensive men and that SBP levels, not DBP levels, predict risk independent of age. After adjustment for age, associated risk factors, and DBP, and compared with subjects with SBP under 140mmHg, the risk ratio for cardiovascular disease mortality was 1.81 in men with SBP between 140mmHg and 160mmHg and 1.94 in men with SBP over 160mmHg. Researchers also report that, after adjustment for SBP levels, cardiovascular disease risk was not associated with DBP.

In the March issue of *Circulation*, vol 105, researchers analyzed the effect of metoprolol CR/XL in women in the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF, total of 3,991 women with heart failure and LVEF of less than 40%), looking at a subgroup of 898 women with severe heart failure, focusing on total death and hospitalization. The investigators found a 21% overall reduction in death and hospitalization per patient per year in the metoprolol CR/XL group compared to the placebo group. There was a 19% reduction in all-cause hospitalization in women, a 29% drop in cardiovascular-related hospitalization, and 42% fewer hospitalizations for heart failure. The researchers also pooled data from two other large studies, the Cardiac Insufficiency Bisoprolol Study (CIBIS-II) and the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS), to analyze overall survival benefits of the three beta-blockers for women. The investigators reported that in women, the three beta-blockers (metoprolol CR/XL, bisoprolol, and carvedilol) increased total survival similar to that of men.

Published in the March issue of *Archives of Internal Medicine*, vol 162, a prospective study on alcohol consumption and the risk of chronic hypertension in young women found that light alcohol drinkers have a slight decrease in the risk of developing chronic hypertension and that heavy drinkers have an increased risk. Researchers from Brigham and Women's Hospital, Massachusetts General Hospital and Harvard University studied a cohort of women from the 1989 Nurses Health Study II, excluding women with hypertension or other illnesses and those who gave birth during follow-up. The researchers reported that women who consume an average of 0.26 to 0.50 drinks per day had a 14% lower risk of developing hypertension compared with non-drinkers. They also reported that an increased risk of hypertension was evident beyond consumption of two drinks per day, but when episodic drinkers (more than 10.5 drinks over 3 or fewer days per week) were separated from the analysis, elevated risk was evident among regular drinkers who consumed more than 1.5 drinks per day.

A study funded by the U.S. Agency for Healthcare Research and Quality (AHRQ) found that the percentage of patients with heart disease who report taking aspirin regularly increased from 59% to 81% between 1995 and 1999. The article was published in the March 15th issue of the *American Journal of Cardiology*. Researchers surveyed more than 25,000 patients from the Duke University Medical Center Databank for Cardiovascular Diseases. Patients more likely to take the drug were younger males, nonsmokers, and those who had suffered prior heart attacks or undergone revascularization procedures in which clogged arteries



"If spring came but once in a century, instead of once a year,
or burst forth with the sound of an earthquake, and not in silence,
what wonder and expectation there would be in all hearts to behold the miraculous change!"
~ Henry Wadsworth Longfellow

The Medication Use Review (MUR) Committee, with representatives from the medical staff, nursing, clinical pharmacy, and nutrition, recently reviewed the following results of a patient telephone questionnaire on *Allegra*.

Allegra Patient Telephone Questionnaire

Conducted: February 2002

Prepared by: Rhonda Eustice, PharmD
Connie Stroll, CPhT

Purpose: It was discovered on the first MUR Committee Disease Review of Allergic Rhinitis that the use of nasal steroids (first-line agents, drugs of choice for allergic rhinitis) were not being optimized by EACH providers. Since that time, *Zyrtec* (cetirizine) has been taken off the EACH formulary. This patient telephone questionnaire was conducted to evaluate the efficacy of *Allegra* (fexofenadine) and to determine how nasal steroids are being used by patients.

Number: 60 patients

Service: FPC/PACC – 24 patients (40%)
IMC – 33 patients (55%)
EENT – 3 patients (5%)

Results:

Allegra:

- 60 patients (100%) tried *Allegra*
- 12 patients (20%) are on an oral antihistamine only
- 48 patients (80%) are on an oral antihistamine and nasal steroid concurrently
- 42 patients (70%) were switched from *Zyrtec*
- ***patient-reported effectiveness***
  - 43 patients (72%) reported that *Allegra* is effective
  - 12 patients (20%) reported that *Allegra* is "O.K", but would prefer *Zyrtec*
  - 5 patients (8%) reported that *Allegra* was ineffective

Nasal Steroids:

- 3 patients (5%) never tried a nasal steroid
- 9 patients (15%) discontinued use of nasal steroid
- 48 patients (80%) were on nasal steroids
  - 65% report using nasal steroid "*only when they really need it*"

Costs: *Allegra* 60mg bid = $31.80 per month
Allegra 180mg qd = $15.90 per month
Flonase = $13.65 per month

Conclusions:

- Patients are **not maximizing** the use of nasal steroids as 65% of patients reported using them on a "prn" basis.
- Monotherapy with nasal steroids used appropriately can decrease costs to EACH and improve symptoms.
- *Allegra* 180mg daily is more cost effective than 60mg twice daily.

Recommendations for Providers:

1) **Please counsel your patients to use their nasal steroids on a daily basis**
2) **Use *Allegra* 180mg daily instead of 60mg twice daily**

Guidelines for the Treatment of GERD
USA MEDDAC, Fort Carson
January 2002

Always prescribe **lifestyle modifications** before medications.

If a provider follows this stepwise treatment it will be considered a preapproved special purchase request and no paperwork will be required. The Gstroenterology Service is exempt from these guidelines.

Rabeprazole (*Aciphex*) 20mg once a day for 30 days ($ 0.22 per day).

If failure to control

Rabeprazole (*Aciphex*) 20mg either twice a day or 2 tablets once a day for 30 days ($ 0.44 per day)

If failure to control

Lansoprazole (*Prevacid*) 30mg once a day for 30 days ($0.98 per day)

If failure to control

Omeprazole (*Prilosec* or generic) 20mg once a day for 30 days ($2.09 per day) – **nonformulary (internal use only)**

Omeprazole (*Prilosec* or generic) 40mg once a day ($3.16 per day) – **nonformulary (internal use only)**

Long term prescriptions (up to 90 days at a time with refills) may be ordered for any of the above treatments once reduction/control of symptoms is achieved.

Patients need to be instructed that they will only be able to get refills for omeprazole at this facility. ***This product is nonformulary and not available at other MTFs in the area.***

Failure to follow this stepwise procedure will result in the patient being sent back to the provider for a special purchase request.